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## CASE REPORT

# AMERICAN CUTANEOUS LEISHMANIASIS WITH UNUSUAL CLINICAL PRESENTATION AND RESPONSE TO TREATMENT

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## SUMMARY

The clinical manifestations and prognosis of cutaneous leishmaniasis (CL) can be influenced by the immune response of the patient and the species of the parasite. A case of atypical clinical presentation of CL, with development of non-characteristic lesions, poor response to therapy, and a long time to resolution is reported. Confirmatory laboratory tests included parasite detection, indirect immunofluorescence, Montenegro skin test, polymerase chain reaction, and parasite identification by multilocus enzyme electrophoresis. The parasite was identified as *Leishmania braziliensis*. The lesion was unresponsive to three complete courses of N-methylglucamine antimoniate intramuscular, and to treatment with pentamidine. The patient did not tolerate amphotericin B. The lesion finally receded after treatment with intravenous N-methylglucamine antimoniate. It is essential to ensure the accuracy of diagnosis and the appropriate treatment, which can include the use of a second choice drug or a different route of administration.

**KEYWORDS:** *Leishmania braziliensis*; Cutaneous leishmaniasis; Unusual clinical forms; Treatment.

## INTRODUCTION

American cutaneous leishmaniasis (ACL) is a major public health problem in the New World. Clinical presentation and outcome of ACL are associated with the host immune response and the infecting *Leishmania* specie<sup>1</sup>. In Brazil, cutaneous leishmaniasis (CL), mainly caused by *Leishmania (Viannia) braziliensis*, is one of the dermatological diseases that deserves more attention due to its magnitude, as well as the risk of deformities and psychological involvement<sup>2</sup>.

The most common clinical form is the classical ulcer, with an indurate raised outer border and sharply incised central crater that usually self-heals over a period of months. The usual clinical presentations of leishmaniasis are easily diagnosed by clinicians in endemic regions, but unusual forms may give rise to difficulties in the diagnosis and appropriate treatment<sup>2</sup>. Cutaneous leishmaniasis can produce a large variety of atypical and rare forms. There has been an increase in the number of papers reporting unusual clinical presentations, both for the Old and the New World<sup>3,4,5,6,7,8,9</sup>.

Meglumine antimoniate is considered the first choice drug for CL treatment in Brazil. The Ministry of Health recommends 10–20 mg/kg Sb<sup>5+</sup> per day for a period of 20 days, by intravenous or intramuscular

route. If no remission is observed, a new treatment cycle is administered for 30 days. In the absence of therapeutic response, the second choice drugs, amphotericin B or pentamidine, are used<sup>2</sup>. Despite pentavalent antimonials (Sb<sup>5+</sup>) be considered first-line drugs used to treat CL caused by different species, an increase in treatment failure has been documented in several regions of the world<sup>10</sup>.

We report a case of a patient with an unusual clinical form of cutaneous leishmaniasis with poor response to antimonial therapy and development of non-characteristic lesions. The present study received approval from the Permanent Committee for Ethics in Research Involving Humans (Process No. 533/2009) of the *Universidade Estadual de Maringá*. The patient agreed to participate in the study and signed a free informed consent form. Written consent was obtained from the patient and his wife for this publication.

## CASE REPORT

A forty-five-year-old black male patient from Apucarana, Paraná, with one atypical lesion on the right side of his back was attended, in March 2009, in the LEPAC (*Laboratório de Ensino e Pesquisa em Análises Clínicas*) of the *Universidade Estadual de Maringá*, for cutaneous leishmaniasis (CL) laboratory diagnosis. The patient

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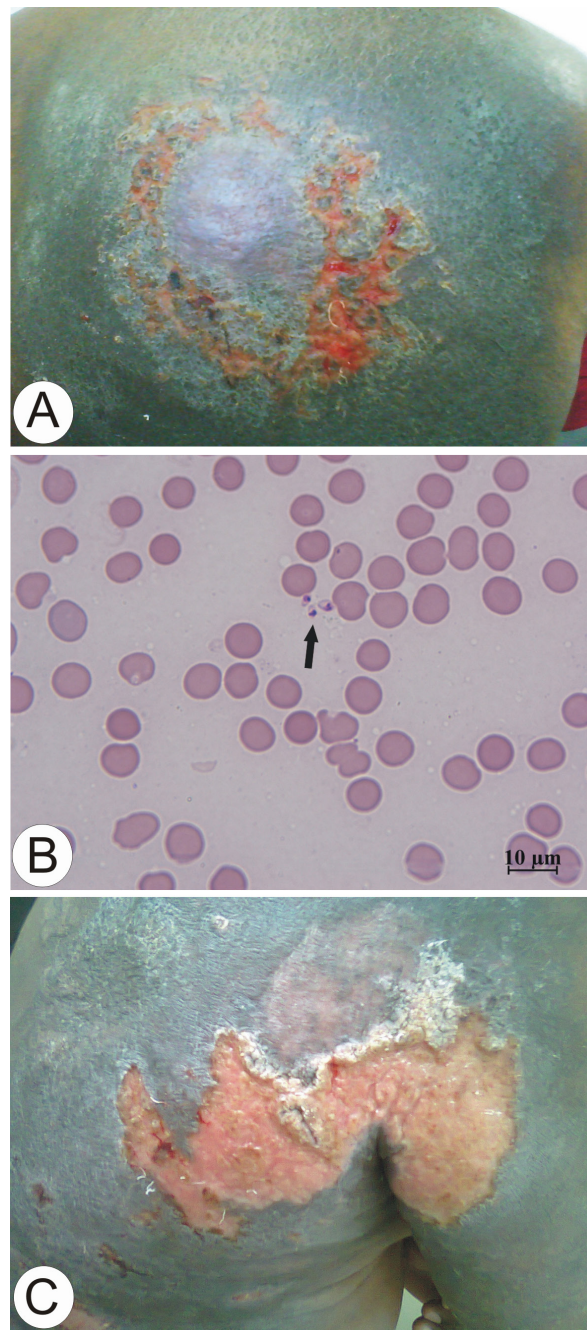
reported that the lesion had been present for approximately one month (Fig. 1A). The lesion was a rounded plaque, with a erythematous violaceous center, descamative ulcerated edges, surrounded by an extensive area of lichenification, measuring 20 cm. Based on clinical appearance, the differential diagnosis of the lesion included chronic simple lichen, psoriasis, squamous cell carcinoma, chromomycosis, cutaneous tuberculosis, syphilis, paracoccidioidomycosis, and sarcoidosis. Before seeking for medical attention, the patient used topical antibiotics, but the lesion persisted without improvement. The performed tests showed a positive Montenegro skin test (MST) with an induration of 10 mm and indirect immunofluorescence (IIF) positive for anti-*Leishmania* IgG antibodies, reaching a titer of 80. *Leishmania* amastigotes were detected in the material obtained by scraping of the lesion stained by Giemsa (Fig. 1B) and cultured in blood base agar (BBA). The BBA grown parasites were sent to the *Coleção de Leishmania* of Instituto Oswaldo Cruz (CLIOC), Rio de Janeiro, Brazil, for identification and the strains were confirmed as *L. (V.) braziliensis* (MHOM/BR/2009/3476). The species identification was performed by multilocus enzyme electrophoresis (MLEE). To exclude the possibility of coexisting infections, fungi and HIV investigations were performed with negative results.

The patient was treated with 120 ampoules of intramuscular meglumine antimoniate (approximately 15 mg/kg Sb<sup>5+</sup> per day) in three cycles of 20 days each at the *Pronto Atendimento Municipal* of Apucarana municipality. Approximately 40 days after the end of treatment (August 2009) the lesion was still active and new laboratory tests were performed. The IIF test was positive with a titer of 160 and the direct parasite search was negative.

About six months later (May 2010) the patient was submitted to another treatment with intravenous pentamidine (4 mg/kg per day) for seven days, which resulted in apparent healing of the lesion. In June 2010, the values of serum amylase (87 U/L) and creatinine (1.0 mg/dL) were normal. However, some months later, new papular lesions emerged, ulcerated and spread to the axillary region. In November 2010, the patient was admitted for treatment with amphotericin B desoxycholate (50 mg/day). The treatment was discontinued after three doses because the values of serum urea (88 mg/dL) and creatinine (3.1 mg/dL) were increased indicating renal failure. One additional course of pentamidine for 10 days was established (April 2011). There was a partial clinical resolution of lesions with the patient still presenting some residual lesions.

In February 2012, about three years after the onset of the lesion and despite the multiple treatments, the lesion was not healing. The lesion was an ulcerated plaque with erythematous fibrous bottom and verrucous edges, surrounded by a lichenification area in the right scapular region and posterior region of the right arm (Fig. 1C). New laboratory tests were performed. The direct parasite search revealed the presence of characteristic amastigotes of *Leishmania* spp., the IIF showed titer 320, and the polymerase chain reaction (PCR) for kDNA minicircles of the subgenus *Leishmania* (*Viannia*) was positive.

The patient was treated again with meglumine antimoniate by the intravenous route (3 ampoules per day) for approximately 40 days. Following this treatment, the lesion healed. Unfortunately, about a year after the end of the treatment, the patient died of a heart attack.



**Fig. 1 -** (A) Initial lesion (one-month-old) on the right back of the patient. (B) Positive direct parasite search with characteristic amastigotes (arrow). (C) The lesion after meglumine antimoniate (120 ampoules), pentamidine, and amphotericin B treatments.

## DISCUSSION

This report describes an unusual case of CL due to the clinical presentation. There was the development of non-characteristic lesions, poor response to therapy and a long time to resolution. The patient was referred to laboratorial diagnosis of CL because, although he lived in an urban area, he had worked in a rural area, near a dam in an endemic

region of CL. According to the patient, the lesion had been present for approximately one month despite presenting 20 cm.

Laboratory diagnosis confirmed the clinical suspicion of CL, with positive results in the direct search of parasites, with few amastigotes in the examined slides, presence of IgG antibodies and positive MST. The antibody search tests are sensitive and specific, but they are associated to cross-reactivity with other diseases, mainly Chagas disease and visceral leishmaniasis<sup>2,11</sup>. MST does not differentiate current and past disease (most often remains positive after treatment) and does not distinguish between infection and disease. MST presents an estimated 84% positivity in the cutaneous form of CL<sup>11</sup>.

In the New World, about fifteen species of *Leishmania* were found in humans causing CL<sup>12</sup>. The three main species causing CL in Brazil are *L. (V.) braziliensis*, *L. (V.) guyanensis* and *L. (L.) amazonensis*<sup>2</sup>. According to WHO, the CL clinical forms include localized, disseminated, diffuse, and atypical cutaneous and mucocutaneous leishmaniases<sup>12</sup>. Many factors can influence the clinical manifestations and prognosis of leishmaniasis, such as the immune response of the patient and the species of the parasite<sup>1,13</sup>. The parasite was identified as *L. (V.) braziliensis*, a prevalent species in southern Brazil and widely distributed in the country<sup>2</sup>. This species can induce a wide spectrum of clinical and immunopathological manifestations<sup>14</sup>.

Atypical lesions of cutaneous leishmaniasis caused by different species of *Leishmania* has been reported. ADRIANO *et al.*<sup>3</sup> reported a case of an unusual presentation of American tegumentary leishmaniasis involving a solitary lesion on the ear lobe, without ulceration. CALPOVINA *et al.*<sup>4</sup> described three distinct variants of CL (erysipeloid, recidiva cutis (LRC), and disseminated leishmaniasis (DL) in children, caused by *L. (V.) panamensis*. TURETZ *et al.*<sup>15</sup> described patients with disseminated leishmaniasis of acneiform, papular, nodular, and ulcerated types, caused by *L. (V.) braziliensis*. NEITZKE-ABREU *et al.*<sup>16</sup> have also reported a case of CL with atypical clinical manifestations due to *L. (V.) braziliensis*. SANDOVAL-JUAREZ *et al.*<sup>9</sup> described an unusual clinical manifestation of CL caused by *L. amazonensis*, in a child that was treated with antimony, had partial remission of some lesions, and reactivation of the lesions following a chronic course.

In the case reported in the present study, the lesion was an atypical clinical form and was still active after three cycles of meglumine antimoniate administered intramuscularly. The peculiarity of this case of leishmaniasis with lesion in form of rounded plaque, descamative ulcerated edges, erythematous violaceous center, and presenting an extensive area of lichenification around the lesion, are uncommon clinical manifestations in CL.

In atypical cases of CL, it is important to rule out the possibility of co-infections. CL in AIDS patients in the New World shows multiple, polymorphic and relapsing lesions<sup>12</sup>. In this case, co-infection with HIV was discarded, thereby to fungal infection.

Despite the apparent healing after treatment with intravenous pentamidine, new papular lesions emerged, ulcerated and spread to the axillary region. The patient was treated with amphotericin B. The treatment was discontinued because the patient showed alterations in renal function tests. An additional course of pentamidine was

administered, there was a partial clinical resolution of lesions, but some residual lesions remained. About nine months after, the lesion was an ulcerated plaque, reaching the right scapular region and posterior region of the right arm. Since there was no successful treatment with second-line drugs available, meglumine antimoniate was used again, but intravenously. Although there is no difference between the intramuscular and intravenous routes, as regards the efficacy and safety of the drug<sup>3</sup>, the lesion finally receded after treatment with meglumine antimoniate administered intravenously.

Despite pentavalent antimonials (Sb<sup>5+</sup>) being considered first-line drugs used to treat CL caused by different species, an increase in treatment failure has been documented in several regions of the world<sup>4</sup>. Studies conducted in Latin America have reported failure in CL treatment with this drug: 7% in Bolivia<sup>17</sup>, 16% in Brazil<sup>1</sup>, and up to 39% in Colombia<sup>18</sup>. GUIMARÃES *et al.*<sup>19</sup> described two cases of atypical ACL that healed after three courses of antimony (15-20 mg/kg/day intravenously for 20 days) and 13 cases healed with amphotericin B, after failure of three or more courses of antimony. PIMENTEL *et al.*<sup>20</sup> reported a similar case of cutaneous leishmaniasis where the lesion relapsed following two systemic treatments with meglumine antimoniate. The patient was treated with amphotericin B, which was interrupted due to poor tolerance. Afterwards, the patient was submitted to intramuscular pentamidine, and no relapse was observed.

An atypical clinical form of CL with a difficult treatment response and a long time to resolution was the main contribution of this study. Reports of unusual and rare clinical forms of CL are relevant to physicians and researchers finding out what *Leishmania* species are capable of, causing forms of difficult diagnosis and treatment. Moreover, the knowledge of these cases is essential to ensure the accuracy of diagnosis and the appropriate treatment of the patient, which can include the use a second-line drug or a different route of administration for the first-line drug.

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